A METHOD OF DETERMINING

THE INITIAL DOSE OF VITAMIN D COMPOUNDS

This application claims priority to U.S. provisional application Serial No. 60/240,126, filed October 13, 2001.

Field of the Invention

The present invention is directed to a method for determining the initial dose of vitamin D compounds when used for the treatment of secondary hyperparathyroidism and renal osteodystrophy. The present invention also is directed to the administration of an initial dose of a vitamin D compound wherein the dose is determined following the method of the invention.

Background of the Invention

Renal osteodystrophy, which encompasses a host of metabolic and morphologic abnormalities of the bone, is an early complication of kidney disease. Elevation of intact parathyroid hormone (iPTH; used interchangeably with "PTH") secondary to renal failure (also referred to as secondary hyperparathyroidism) is a major contributor to high-turnover renal osteodystrophy. The various disorders of bone formation with high-turnover renal osteodystrophy may be accompanied by such conditions as fractures and bone deformities, bone cysts, osteopenia, resistance to erythropoietin caused by marrow fibrosis, intractable pruritus, spontaneous tendon rupture, periarthritis and joint pain, myopathy, growth failure in children, and extraskeletal calcification.

Through appropriate monitoring and treatment, many patients with secondary hyperparathyroidism from renal failure can maintain mobility and physical function

and circumvent the need for surgical parathyroidectomy. Apart from dialysis, such treatment may include the use of vitamin D compounds such as calcitriol and paricalcitol.

Calcitriol (also referred to as $1,25\text{-}(OH)_2D_3$; $1\alpha,25\text{-}(OH)_2D_3$; 1,25 dihydroxycholecalciferol or 1,25 dihydroxy vitamin D) is a vitamin D_3 analog and is the metabolically active form of vitamin D. Paricalcitol (also referred to as 19-nor $1,25\text{-}(OH)_2D_2$ or 19-nor 1,25 dihydroxy vitamin D_2) is a vitamin D_2 derivative. Both compounds suppress PTH levels with minimal effect on calcium and phosphorus levels. These compounds have been approved and marketed in the United States for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure in adults. These approvals were based on the results of controlled clinical trials performed in patients with end-stage renal disease (ESRD). The currently approved starting dose of calcitriol injection (CALCIJEX®, Abbott Laboratories) is 0.02 microgram/kilogram dry weight (mcg/kg) and for paricalcitol injection (ZEMPLAR®, Abbott Laboratories), 0.04 mcg/kg.

Currently, the first or starting dose for patients undergoing treatment for secondary hyperparathyroidism is based on the weight of the patient. Many pharmatherapies recommend initial drug dosing to be based upon weight. These recommendations are derived from the need to reach therapeutic levels based upon the distribution of the medication throughout the patient's body fluid compartment. The approximate amount of this fluid can be determined based upon the patients body weight. However, patients with secondary hyperparathyroidism as a result of ESRD have large fluctuations in body weight due to their inability to eliminate excess fluid via the kidneys. Fluctuations may be as little as 1 kg daily to as much as 20 kg daily.

Therefore, attempts to prescribe a starting dose of a vitamin D compound based upon the current weight often prohibits accurate estimation.

Dosing of vitamin D compounds based on a range of PTH provides an alternative to the approach based on weight. However, the published ranges require interpretation by the attending medical professional and do not address patients with severe elevated levels of PTH. Thus, while the published ranges are considered safe they may not be necessarily efficacious.

Inaccurate estimations of starting doses for vitamin D therapy may delay effective treatment of secondary hyperparathyroidism. Such delays have been associated with prolonged elevations of PTH and the resultant altered metabolism. These alterations, often resulting in hypercalcemia and/or hyperphosphatemia, put patients at risk for cardiovascular complications. (Blcok, 2000; Goodnew 2000)

Thus, there is an ongoing need for improved dosing schedules for vitamin D compounds when used to treat renal osteodystrophy and/or hyperparathyroidism. We have discovered an easy to use method to determine the safe and efficacious starting dose for patients commencing treatment of secondary hyperparathyroidism. This dosing scheme allows a patient to receive an initial dose of vitamin D based on the patient's PTH level as opposed to the current approved method based on body weight.

Summary of the Invention

One aspect of the present invention provides a method of determining the initial dose of a vitamin D compound. The method utilizes the final dose as a response variable and baseline PTH as a predictor variable. Both variables can be determined from existing data, typically data generated from clinical trials. Regression analysis is performed on the data to generate the initial dose.